

### **REMARKS/ARGUMENTS**

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, Claims 58-77 were pending in this application. With this amendment, Claims 63-66 and 68-69 have been amended to clarify what Applicants have always regarded as their invention, Claims 58-62, 64-65, 67 and 71-73 have been canceled without prejudice and new Claims 78-84 have been added.. Claims 63, 66, 68-70 and 74-84 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. New Claims 78-84 are fully supported by the specification and the claims as originally filed. Support for new Claims 78-84 can be found in the specification at least, for example, on page 108, lines 8-16 and on page 129, line 35 to page 130, line 5.

In addition, Applicants request the PTO to take note of the Revocation and Power of Attorney and Change of Address filed on March 7, 2003, and kindly direct all future correspondence to the address indicated, *i.e.*, to:

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### **Specification**

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code.

Further, Applicants have amended the specification to correct the ATCC address on page 372, line 34 and the paragraph beginning at page 374, line 32, has been amended to comply with the provisions of the Budapest Treaty.

### **Double Patenting**

The pending claims stand rejected under double patenting. In particular, the Examiner alleges that "there is at least one other application filed by the applicants which contains the polypeptide of SEQ ID NO: 15 which is identical to the polypeptide of SEQ ID NO: 6, and which contain possible conflicting claims." The Examiner further states that "applicant is required to point out to the Examiner all double patenting issues."

To our best knowledge, Applicants have not filed any applications having claims directed to a polypeptide of a sequence identical to SEQ ID NO: 6. Applicants believe that the Examiner reached his conclusion of the existence of possible conflicting claims based on the disclosure of the **publications** of other U.S. applications filed by Applicants, which do not reflect the changes made in preliminary amendments in those applications:

Accordingly, Applicants request that claim rejections under double patenting be withdrawn.

### **Formal Matters**

Applicants thank the Examiner for acknowledging that the deposit of organisms under accession number ATCC 209786 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure is in compliance with the deposit requirement.

### **Priority Determination**

The Examiner asserts that the effective filing date for the application is October 24, 2001, the actual filing date of the instant application, and that Applicants are not entitled to claim priority to earlier-filed applications because they do not meet the requirements of 35 U.S.C. §112, first paragraph.

As discussed below, Applicants rely on the gene amplification assay (Example 114) for patentable utility which was first disclosed in International Application No. PCT/US00/03565, filed February 11, 2000, priority to which has been claimed in this application.

As will be shown, the disclosure of the instant application, which is similar to that of the earlier-filed application, provides the support required to establish utility for the nucleic acid

encoding the PRO274 polypeptide and the nucleic acid of SEQ ID NO:6. Hence, Applicants respectfully submit that the effective filing date of the present application is February 11, 2000.

In support, Applicants enclose herewith pages 138-163, describing the gene amplification assay (Example 26), of WO 01/53486, corresponding to PCT Application PCT/US00/03565.

**Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)**

Claims 58-77 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." The Examiner specifically notes that "[t]here is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO274." Further, the Examiner asserts that because PRO274 was amplified in only a very small number of tumors of the same type, for example, one (LT4) out of nine human lung tumor adenocarcinoma tumors and two (LT16 and LT18) out of nine human lung tumor squamous cell carcinomas, "the data do not support the implicit conclusion of the specification that PRO274 shows a positive correlation with lung cancer, much less that the levels of PRO274 would be diagnostic of such."

Claims 58-77 are further rejected under 35 U.S.C. §112, first paragraph, allegedly because one skilled in the art would not know how to use the claimed invention "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

For the reasons outlined below, Applicants respectfully disagree and traverse the rejections.

Applicants submit that the cancellation of Claims 58-62, 64-65, 67 and 71-73 renders the rejection of these claims moot. With respect to Claims 63, 66, 68-70 and 74-77, Applicants submit, as discussed below, that the Examiner has not established a *prima facie* case for lack of utility for PRO274 polypeptide.

**Utility – Legal Standard**

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has

at least one asserted “specific, substantial, and credible utility” or a “well-established utility.”

Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. **“Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a “substantial” utility.”** (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II (B) (1) gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, the Utility Guidelines restate the Patent Office’s long established position that any asserted utility has to be “credible.” “Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant’s assertions.” (M.P.E.P. §2107 II(B)(1)(ii)). Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The PTO also sets forth the evidentiary standard as to utility rejections. In general, an Applicant’s assertion of utility creates a presumption of utility that will be sufficient to satisfy the

utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. §101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

#### **Proper Application of the Legal Standard**

Applicants submit that the invention defined by the presently amended claims has specific, substantial and credible utility for the nucleic acids encoding the PRO274 polypeptide.

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 114 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9, including primary lung cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9. Further, Example 114 explains that the results of TaqMan™ PCR are reported in  $\Delta C_t$  units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc. PRO274 showed approximately 1.00-1.61  $\Delta C_t$  units which corresponds to  $2^{1.00}$  -  $2^{1.61}$  fold amplification or 2.0 fold

to 3.053-fold amplification in three types of human primary lung tumors, which is significant and thus the PRO274 gene has utility as a diagnostic marker of lung cancer.

Regarding the Examiner assertion that because PRO274 was amplified in only a very small number of tumors of the same type, the data did not support the implicit conclusion of the specification that PRO274 showed a positive correlation with lung cancer, much less that the levels of PRO274 would be diagnostic of such, Applicants respectfully disagree.

In response, Applicants respectfully submit a Declaration signed by Dr. Thomas D. Wu. Dr. Wu studied microarray data from various types of human lung tumors for PRO274 mRNA expression levels. In particular, types of lung tumors Dr. Wu studied included (1) squamous cell carcinoma, (2) adenocarcinoma, (3) carcinoma, large cell, (4) carcinoma, small cell and (5) carcinoma, unspecified non-small cell.

As stated in the Declaration, Dr. Wu found that for each type of the lung tumor listed above, the mRNA expression level of PRO274 was at least 10% or greater in the lung tumor tissues compared to normal lung tissues. Furthermore, on page 3 of the Declaration, Dr. Wu states:

It is my considered opinion that when, the mRNA of a gene is overexpressed in at least about 10% of the lung tumors of the same type, the gene is biologically significant as a lung tumor marker. It is well known in the art that a lung tumor marker that is uniformly expressed in each type of lung tumor is very rare. Therefore, a gene that is overexpressed in at least 10% of a type of lung tumor would have a positive correlation with lung tumors.

Therefore, Dr. Wu concludes:

It is my considered scientific opinion that identifying patients having a gene, such as PRO274 gene that is overexpressed in at least 10% of the lung cancer patients, would provide significant information for diagnosis and treatment since it would enable more accurate tumor classification and hence better determination of a suitable therapy.

Further, Applicants submit that the cell surface markers vary among the different types of tumor cells and cell lines. Some PRO polypeptides may be tested positive in a majority of the tested tumors and tumor cell lines, suggesting that they function as universal lung tumor markers for a variety of types lung tumors. On the other hand, some PRO polypeptides, such as PRO274,

may be tested positive only in a limited number of lung tumors and tumor cell lines. As Dr. Wu suggested in his Declaration, a universal lung tumor marker is very rare. Accordingly, Applicants respectfully submit that genes encoding PRO polypeptides, such as PRO274, that are only amplified in a limited number (*i.e.*,  $\geq 10\%$  of the samples) of lung tumors can still be used as a cancer marker. Accordingly, Applicants believe that the Examiner has erroneously concluded that the present data do not support a correlation between PRO274 and lung tumor.

Applicants respectfully submit that it is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 114 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO274 is a diagnostic marker of human lung cancer.

Accordingly, the claimed invention has a specific, substantial and well established utility that is well described in the specification.

Applicants respectfully submit that based on the teachings of Example 114 and the general knowledge available in the art at the priority date of the invention, one skilled in the art would be able to practice the claimed invention in its full scope without any undue

experimentation. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff. sub nom.*, *Massachusetts Institute of Technology v A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. §2164.01.

Furthermore, based on the instant disclosure and the advanced knowledge in the art at the time of filing, one skilled in the art would know exactly how to make and use these nucleic acids for the diagnosis of lung tumors; for example, by using diagnostic methods based on hybridization to such amplified sequences.

In view of the above, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

**Claim Rejections – 35 U.S.C. §112, First Paragraph (Written Description)**

Claims 58-62 and 71-77 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of sufficient written description. The Examiner asserts that claims drawn to "nucleic acid having at least 80%, 85%, 90%, 95% or 99% identity" to the nucleic acid of SEQ ID NO:6, but the claims do not require that the nucleic acid or encoded polypeptide possess any particular biological activity, conserved structure or other distinguishing feature. Thus, the Examiner notes that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Applicants submit that the cancellation of Claims 58-62, 64-65, 67 and 71-73, and amendment to Claim 74 (and, as a consequence, those claims dependent from the same) to be dependent on Claim 63 render the rejection of these claims moot.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of Claims 74-77 under 35 U.S.C. §112, first paragraph.

**Claim Rejections – 35 U.S.C. §112, Second Paragraph**

Claims 71-73 are further rejected under 35 U.S.C. §112, second paragraph, because the term "stringent" conditions is indefinite.

Without acquiescing to these rejections, Applicants submit that the cancellation of Claims 71-73 renders the rejection of these claims moot. Accordingly, Applicants request that the rejection of Claims 71-73 under 35 U.S.C. §112, second paragraph, be withdrawn.

**Claim Rejections – 35 U.S.C. §102(b)**

The Examiner noted that the priority of the instant application is set at October 24, 2001. As discussed above, Applicants respectfully submit that the effective filing date of the present application is February 11, 2000.

Claims 58-67 and 71-76 are rejected under 35 U.S.C. §102(b) as being anticipated by Ho *et al.*, Science, Vol. 289, pp 265-270 (publication date July 14, 2000). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the cancellation of Claims 58-62, 64-65, 67 and 71-73 renders the rejection of these claims moot.

As discussed above, the pending claims of the instant application are entitled to the effective filing date of February 11, 2000, and hence, Ho *et al.* is not prior art under 102(b) since its publication date is after the effective priority date of this application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

**Claim Rejections – 35 U.S.C. §103(a)**

Claims 69-70 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ho *et al.* in view of Hopp *et al.*, U.S. Patent No. 5,011,912. Applicants respectfully traverse this rejection.

As discussed above, Applicants are entitled to the effective filing date of February 11, 2000. Therefore, the primary reference, Ho *et al.* is not prior art. Thus, Applicants respectfully submit that the instant claims are not obvious over Ho *et al.* in view of Hopp *et al.* Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.


**CONCLUSION**

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C64**).

Respectfully submitted,

Date: November 18, 2004

By:   
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